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(54) Anti-bacterial polymeric materials

(57) Polymeric materials suitable for use in making extended wear contact lenses have covalently bound to the polymer backbone substituents possessing anti-bacterial activity. Such polymers may be derived by polymerising a monomer mixture which includes a monomer having a substituent possessing anti-bacterial activity. Exemplified anti-bacterial monomers are prepared by reacting acryloyl chloride with 2,6-dibromo-4-aminophenol, 2,6-dibromo-4-hydroxyphenol or 2,4-dihydroxybenzophenone; and by reacting allyl bromide with 2,6-dibromo-4-hydroxyphenol.

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## SPECIFICATION

**Hydrogel forming polymeric materials**

5 This invention relates to polymers having anti-bacterial properties, and more particularly to the use of such polymers in the production of biomedical materials. 5

The need for effective sterilisation of biomedical materials, for example, those used in plastic contact lenses is well known. For many years antiseptic solutions have been used to provide sterilisation of hard lenses. However, the use of such solutions with soft plastic contact lenses is 10 undesirable since residues of the solution, left in the material, can be leached out and cause irritation to the eye. It is well known that the build-up of conventional sterilisation solutions in soft plastic contact lenses are considerable. A regime of boiling can be used but this is not a complete answer as boiling can cause proteins to denature and adhere strongly to the contact lens. This creates a potential for lens discomfort, poor vision and irritation. Furthermore, when 15 the sterilised contact lens is removed from its case for insertion into the eye, recontamination with bacteria from the fingers is very likely. 15

It has now been found that the incorporation of substituents possessing anti-bacterial activity into a polymer material can impart anti-bacterial properties to the surface of the polymer.

Accordingly, the present invention provides a polymer material comprising a polymer having 20 covalently bound to the polymer backbone substituents possessing anti-bacterial activity. 20

The invention further provides a process for the production of a polymer material which comprises polymerising a monomeric mixture comprising as one component an ethylenically unsaturated compound having a substituent possessing anti-bacterial activity.

Usually only a small quantity of the monomer having a substituent possessing anti-bacterial activity need be included in the polymer, for example, up to 15% by weight, based on the total 25 weight of the monomers, and preferably from 1 to 3% by weight. 25

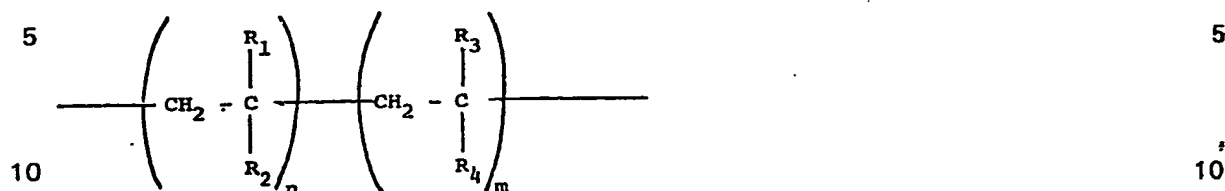
The invention is particularly applicable to the production of water absorbing hydrophilic polymer materials which have a variety of biomedical applications, for example, in the production of soft contact lenses.

30 The substituent possessing anti-bacterial activity may be derived, for example, from a compound having anti-bacterial properties, for example a phenol, such as an alkyl or aralkyl substituted phenol, a halogenated phenol, a halogenated alkyl or aryl substituted phenol, an amino substituted phenol, an amino substituted halogenated phenol, a polyhydric phenol, a halogenated polyhydric phenol, an acridine or an amino substituted acridine, an aryl or aralkyl 35 alcohol, a halogenated alkyl or aryl alcohol, or an organic salt or other derivative of an organic or inorganic acid or amine. Suitable compounds having anti-bacterial properties may include, for example, polyhydric phenols and substituted polyhydric phenols such as 2,6-dibromo-3- 35 hydroxyphenol, 3-hydroxy-4-n-pentylphenol, 3-hydroxy-4-n-octylphenol, 4-chloro-2, 4-dihydroxy-diphenyl-methane, aminophenols and substituted aminophenols such as 2,6-dibromo-4-amino- 40 phenol, 2,4,6-triaminophenol, 2,6-diamino-4-n-pentyl-phenol, 2,6-dinitro-4-aminophenol, cresols 40 such as o-chlorocresol, alcohols and substituted alcohols such as benzyl alcohol, phenyl ethyl alcohol and chlorbutanol, acid and amino derivatives such as chlorhexidine diacetate, methyl, ethyl, and propyl hydroxybenzoate, phenylmercuric acetate, benzalkonium chloride ethylenedi- amino-tetraacetic acid, and thiomersal and cetrimide.

45 An ethylenically unsaturated group may be introduced into compounds having anti-bacterial properties by reaction with an appropriate unsaturated compound, which may, for example in the case of a phenolic compound be an allyl halide, an allyl acid chloride or an allyl amide. Preferably, however, the monomer having a substituent possessing anti-bacterial activity comprises an acrylate or methacrylate group, and these may be introduced by reacting a 50 compound having anti-bacterial properties, with for example acryloyl chloride or methacryloyl chloride. 50

Examples of particularly preferred ethylenically unsaturated compounds having a substituent possessing anti-bacterial activity include for example acryloyl and methacryloyl esters of the above mentioned polyhydric phenols and also acryloyl and methacryloyl amides of the above 55 mentioned aminophenols and substituted aminophenols. 55

The polymers to which this invention can suitably be applied may for example be copolymers of a major proportion of ethylene glycol methacrylate or vinyl pyrrolidone together with a minor proportion of the monomer having a substituent possessing anti-bacterial properties. Preferably, the polymer is a copolymer comprising a major proportion of a non-polar vinyl hydrocarbon 60 monomer and a poly vinyl monomer such as those described and claimed in British Patent No. 1395501. Polymers according to the aforementioned British Patent have the formula: 60



wherein  $R_1$  and  $R_3$  are each independently hydrogen or lower alkyl groups,  $R_2$  is a non-polar hydrocarbon group,  $R_4$  is a polar hydrophilic group and  $m$  and  $n$  are integers such that the polymer is hydrophilic and capable of absorbing water. Where  $R_1$  and  $R_3$  are lower alkyl groups, these may contain a carbon chain having up to six carbon atoms and may be substituted or unsubstituted groups such as for example, methyl, propyl, butyl, pentyl, or hexyl groups. Preferably  $R_1$  and  $R_3$  are each independently hydrogen or methyl groups.  $R_2$  is a non-polar hydrocarbon group which may be a saturated or unsaturated aliphatic or aromatic group, such as for example a methyl, ethyl, propyl, butyl, pentyl, hexyl, decyl, hexadecyl or phenyl group.  $R_2$  is preferably a bulky substituent group and particularly suitable substituent groups have been found to be aryl groups and branched chain alkyl and aralkyl groups such as for example, methyl or phenyl substituted propyl, butyl or pentyl groups.  $R_4$  is a polar hydrophilic group, that is to say, a group conferring hydrophilic properties upon the polymer, and may for example be an oxygen-containing aliphatic group, such as a pyrrolidone group, or more particularly one having a hydroxyl substituent, such as for example, a hydroxyl-substituted ethyl, propyl or butyl group or an aliphatic ester group. Alternatively the polymer may be a copolymer comprising a hydroxyl substituted unsaturated aliphatic compound, an amide of an unsaturated aliphatic carboxylic acid, and an unsaturated aliphatic carboxylic acid or an ester thereof, as described in British Patent Specification Nos. 1,500,692 and 1,566,249. Particularly good results have been obtained using polymers comprising a major proportion of either hydroxypropyl acrylate, vinyl pyrrolidone and styrene, or acrylamide, hydroxypropyl acrylate and ethyl acrylate, together with a minor proportion of the ethylenically unsaturated compound having a substituent possessing anti-bacterial activity.

Even more preferred polymer have been obtained by modifying in accordance with this invention polymeric materials as described in European Patent Application No. 80301136.0, either by including the anti-bacterial monomer additionally or using it to replace part of one or more of the existing monomers. These polymeric materials comprise units derived from the following monomers in the given proportions:

- 1) 20 to 40 mole % of a polymerisable amide which is an unsubstituted amide of a carboxylic acid containing olefinic unsaturation,
  - 2) 25 to 55 mole % of an N-vinyl lactam,
  - 3) 5 to 20 mole % of a polymerisable ester which is an ester of a carboxylic acid containing olefinic unsaturation,
  - 4) 1 to 10 mole %, preferably 1 to 3 mole %, of a polymerisable carboxylic acid containing olefinic unsaturation,
  - 5) 3 to 10 mole %, preferably 5 to 10 mole %, e.g. 7 to 10 mole %, of a polymerisable hydrophobic vinyl monomer,
- the copolymer being cross-linked with a cross-linking agent in an amount of, for example, up to 5, preferably up to 1, weight %, based on the total weight of the monomers.

The olefinically unsaturated carboxylic acid or derivative thereof used in components (1), (3) and (4) is advantageously one containing a vinyl group of structure



and is preferably acrylic or methacrylic acid.

Component (1) may be an amide or acrylic or methacrylic acid, for example, acrylamide, methacrylamide or diacetone acrylamide. This component is present in the copolymer to provide strength and hydrophilicity. It is particularly preferred to use acrylamide alone or together with a mixture of methacrylamide and/or diacetone acrylamide. The latter combination confers a better hydrolytic stability on the material but with a reduced water content compared to acrylamide alone.

The N-vinyl lactam, component (2), is a weakly basic hydrophilic component. The compound may, for example be, N-vinyl pyrrolid-2-one, or an alkyl substituted derivative thereof, for example, N-vinyl-5-methylpyrrolid-2-one, N-vinyl-5-ethylpyrrolid-2-one, N-vinyl-5,5-dimethylpyrrolid-2-one, N-vinyl-5,5-diethylpyrrolid-2-one or N-vinyl-5-methyl-5-ethylpyrrolid-2-one. Excellent results have been obtained with N-vinylpyrrolid-2-one.

Component (3) may be a hydroxy substituted ester of acrylic or methacrylic and is preferably a hydroxy propyl or hydroxy ethyl ester in particular, hydroxy propyl acrylate or hydroxy ethyl methacrylate, the 2-isomers being the more generally used isomers. This component is less hydrophilic than the lactam component; its incorporation reduces the tendency of blocks of the same monomer to form the copolymer and hence facilitates the even distribution of water in the hydrated copolymer matrix.

The unsaturated aliphatic carboxylic acid is present as a hydrophilic component and is capable of hydrogen bonding with the donor groups in the other monomers, thereby adding strength to the material. Thus, in order to achieve an appropriate balance of high water content and high strength, the quantities of the acid incorporated in the copolymer matrix and the N-vinyl lactam not incorporated in the copolymer matrix must be carefully controlled.

It is however, unnecessary for the acid component (4) to be introduced specifically into the mixture of monomers since it may already be present in sufficiently high proportion as an impurity in the hydroxy-substituted ester component (3). An alternative way in which it can be introduced is by conversion of  $\text{CONH}_2$  groups of the amide component (1) to  $\text{COOH}$  groups during autoclaving of the materials. These alternatives are intended to be comprehended within the scope of the invention.

A preferred example of the hydrophobic vinyl monomer is styrene. However, other hydrophobic monomers may be used such as the monoesters of unsaturated aliphatic carboxylic acids, preferably esters of acrylic or methacrylic acid, for example, methyl methacrylate. Preferably styrene alone is used or a part of the styrene is replaced by the latter ester. It is possible by adjusting the amount of the hydrophobic monomer incorporated, to adjust the water content of the material.

The desired small amount of cross-linking can be introduced into the copolymer matrix either during copolymerisation or after the main copolymerisation to form a linear chain has been completed. When the cross-linking is introduced after the main copolymerisation, it can be introduced in a final compression or injection molding process in which the final optical form of the lens is produced. Such a method and suitable cross-linking agents are described in UK Patent Specification No. 1,436,705. In this case, it is desirable that the copolymer should be substantially linear at least prior to moulding so that it can undergo viscous flow under the reaction of heat and pressure above its glass transition temperature and permit the use of compression or injection moulding techniques. The proportion of cross-links introduced into the final copolymer will usually be quite small, preferably 1 to every 10 to 200 repeating polymer units on average and most preferably 1 to every 60 to 100 polymer units.

Examples of suitable cross-linking agents which can be used during the main copolymerisation are the diesters of unsaturated aliphatic carboxylic acids, such as ethylene glycol dimethacrylate and polyethylene oxide (for example of molecular weight 400) dimethacrylate or divinyl benzene. When the cross-linking agent is to be added immediately prior to moulding, it may be a diamide of an unsaturated aliphatic carboxylic acid, an anhydride of an unsaturated aliphatic or aromatic carboxylic acid, a diepoxide or dicumyl peroxide. In the case of such cross-linking agents as ethylene glycol dimethacrylate there may be no necessity to add these specifically since, if hydroxyethyl methacrylate is used as component (3) this may contain sufficient of the diester as impurity to cross-link the material effectively.

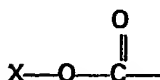
According to a still further preferred embodiment of the present invention, the materials modified in accordance with this invention are the polymeric materials of European Patent Application No. 80301136.0 when themselves modified to reduce protein deposition as described in British Patent Application No. (Our Folio P2620) by incorporation of a controlled amount of fluoroaliphatic side chains. Component 5) from which these materials are derived is 3 to 10 mole %, preferably 5 to 10 mole %, e.g. 7 to 10 mole %, of a hydrophobic monomer component comprising: a) a fluorinated polymerisable monomer having a fluoroaliphatic side chain, and b) a non-fluorinated polymerisable hydrophobic vinyl monomer. Preferably the materials are derived from 1 to 9 mole %, particularly 1 to 5 mole %, of monomer a). Monomer b) corresponds with the hydrophobic monomers (5) of the polymeric materials of European Patent Application No. 80301136.0. The anti-bacterial monomer may be included additionally or used to replace part of at least one of the existing monomers.

The introduction of the fluorinated monomer of component (5) into the polymeric materials may be achieved by polymerising such a monomer having a fluoroaliphatic side chain with the other identified types of monomer. Alternatively, the polymerisation may be carried out with a monomer comprising precursor groups which are esterifiable groups such as hydroxyl groups, and these groups in the polymer can subsequently be esterified, either before or after shaping or

other manner of production of the finished article with a fluorinated aliphatic acid or derivative thereof to provide the necessary fluoroaliphatic side chains attached to the backbone of the polymer.

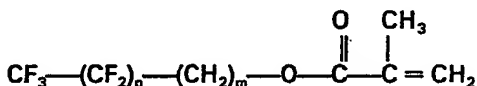
The esterification may be carried out by swelling the polymer in an anhydrous aprotic solvent containing the fluorinated aliphatic acid or derivative thereof. For example a copolymer derived from a hydroxy alkyl acrylate or methacrylate may be reacted in tetrahydrofuran or a similar solvent with trifluoroacetic acid or more preferably the derived trifluoroacetylchloride or trifluoroacetyl bromide. This technique has the advantage that the surface of the polymer may be preferentially treated after shaping into the finished article.

The fluoroaliphatic side chain preferably comprises a fluoroalkyl group, preferably one containing up to about twelve carbon atoms, for example a fluorinated methyl, ethyl, propyl, or butyl group. Highly fluoro-substituted side chains are preferred for the purposes of the present invention, particularly those having a terminal trifluoromethyl group. The most preferred side chains are fluoro-substituted aliphatic ester groups, of the general formula

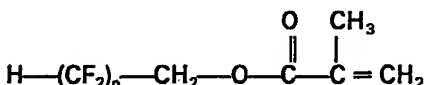


where X represents a fluoro-substituted alkyl group containing up to six carbon atoms, for example, trifluoroethyl, 1,1,7-trihydroperfluoroheptyl, 1,1,5-trihydroperfluoropentyl, 1,1-dihydroheptafluorobutyl, 1,1,3-trihydroperfluoropropyl or, especially, hexafluoroisopropyl.

Specific example of fluorinated monomer, which may according to one embodiment of the invention be reacted to form the polymeric materials, include fluorinated olefins and fluorinated unsaturated alcohols, carboxylic acids and esters. Particularly preferred are the fluoroalkyl esters of unsaturated carboxylic acids, for example esters of acrylic and methacrylic acids. Examples of suitable esters include trifluoroethyl acrylate and methacrylate, hexafluoroisopropyl acrylate and particularly its methacrylate, 1,1,3-trihydroperfluoropropyl methacrylate, perfluoroalkyl alkyl methacrylates of the formula



and fluoro-alcohol methacrylates of the formula



where  $m$  and  $n$  are integers such that the perfluoroalkyl alkyl or fluoro-alcohol group contains up to twelve carbon atoms.

The polymerisation of the materials of the invention may generally be initiated by radical or ionic initiators or catalysts and may be carried out in emulsion, suspension, bulk or solution polymerisation systems. Preferably the polymerisation is carried out in solution in a non-hydroxylic solvent, such as for example dioxan, dimethylformamide or tetrahydrofuran. Preferably the polymerisation is carried out in a medium which is a solvent for the monomers and for the polymer. After reaction the polymer may then be precipitated, for example by pouring the reaction mixture into a liquid which is a non-solvent for the polymer.

The polymerisation reaction mixture may contain up to about 10% e.g. about 1% by weight of the polymerisation catalyst, for example, benzoyl peroxide, azobisisobutyronitrile or lauryl peroxide.

However, in the case of the polymeric materials described in European Application No. 80301136.0, fluorinated modifications of these, and other polymers where suitable, the polymerisation of the components including the anti-bacterial monomer is suitably carried out in a bulk polymerisation system by mixing the monomer initiated by radical initiators or catalysts, or by other radical-generating techniques such as photo initiation for example using u.v. rays. Suitable initiators are t-butyl peroctoate, methyl ethyl ketone peroxide and azobisisobutyronitrile.

In bulk polymerisation, a problem may arise from the fact that polymerisation of acrylamide containing compositions is known to be violent unless mild conditions of polymerisation are used. If however, the polymerisation is slow, this tends to result in rods of uneven composition with distorted (pyramid-like) shape because of side reactions. It has been found that the use of the initiator methylethylketone peroxide can help to produce good quality rods via rapid, yet non-violent polymerisation of acrylamide-containing compositions at low temperatures.

A further problem is caused by the fact that the monomers used in preparing the material

have different reactivity ratios which also vary with the polymerisation conditions, and hence the resulting rods tend to contain residual monomer which gives rise to tackiness and softening of the rod in some cases. Whilst post-cure and heat treatment in a vacuum removes the tackiness, it also inherently causes discolouration of the rods. Immersion and washing of the rods in suitable solvents, e.g. acetone, for 2 hours followed by washing with methanol can overcome the problem of tackiness as an alternative to prolonged post-cure.

The polymerisation reactions, in general, may be carried out at a temperature of from about 50°C to about 120°C or even higher, but preferably the reaction temperature is within the range of from about 60°C to 70°C. Reaction may usually be complete in from about  $\frac{1}{2}$  hour to about 24 hours, depending upon the temperature, the amount of catalyst and the relative proportions of the monomers.

In the case of the polymeric materials described in European Patent Application No. 80301136.0, however, the polymerisation takes place in two distinct stages, firstly gelation which is suitably carried out at a temperature of 40°C to 70°C, but is generally in the range of 60°C to 70°C. The gelation is normally complete within 1 to 4 days e.g. within 48 hours depending upon the temperature used, the nature and amount of the catalyst, the relative proportion of the monomers and the nature of any solvent present. This is then followed by a post-cure which is performed at a higher temperature e.g. 70°C to 100°C, to complete the polymerisation and harden the rod. This latter stage is normally complete in several hours, e.g. up to 10 hours.

After polymerisation the polymer may be treated to remove any residual monomer, solvent or initiator, washed and dried under vacuum.

Another, though less preferred, method for producing the polymer materials is to graft an appropriate substituent group having anti-bacterial properties on to reactive sites on the polymer backbone. The grafting reaction may be carried out by reacting a compound having anti-bacterial properties with a suitably reactive polymer in order to graft a residue of the anti-bacterial compound, retaining the anti-bacterial properties, on to the polymer backbone. This procedure has the advantage that all the anti-bacterial substituents are introduced on to the surface of the polymer, but the reaction is found in practice to be less controllable than the polymerisation reactions previously described.

In an alternative method of processing, the polymer, when suitable, is first compacted into a sheet, and then individual shaped articles are compression moulded from the sheet. Usually the moulding temperature is from 120°C to 300°C and the mould pressure is from 10 lbs per sq. in. to 20 tons per sq. in. At the moulding stage, the polymer may be cross-linked by a suitable cross-linking agent, which is preferably added at the polymerisation stage and activated during moulding. In processing the polymer into a sheet prior to moulding, it is thus important to make sure that the temperature of the sheet is kept below that necessary to activate the cross-linking agent.

Finally, the shaped article is immersed in water or an aqueous medium until equilibrium is reached. The quantity of water absorbed by the polymer depends upon the nature of the polymer and its structure, but preferably the polymer contains from 20% to 90% and most preferably from 60% to 80% by weight of water.

The preferred plastic materials of the present invention have a surface freely wettable by tear fluid and are particularly suitable for the production of contact lenses. They may be made optically clear and have excellent permeability to oxygen and carbon dioxide. The oxygen permeability of the plastic materials may be greater than  $100 \times 10^{-10}$  cc.mm.cm<sup>-2</sup> sec.<sup>-1</sup> cm.Hg<sup>-1</sup> and in some cases may be as high as  $200$  to  $1000 \times 10^{-10}$  cc.mm.cm<sup>-2</sup> sec.<sup>-1</sup> cm.Hg<sup>-1</sup>.

It has been found that the presence of the substituents having anti-bacterial activity in the polymer has a profound effect upon the ability of the polymer to retard bacterial growth upon its surface. In addition to their use in contact lenses, the plastic materials of the present invention may find application as prosthetic implants within the body, for example, blood vessels, artificial ureters, and artificial breast tissue, and as membranes intended to come into contact with body fluids (but outside the body) for example membranes for kidney dialysis and heart/lung machines. The polymer materials may also be useful as wound dressings, nappy liners, swabs and bandages.

In addition to their anti-bacterial activity, some of the monomers used in this invention have the further advantage that they can also act as anti-oxidants for the polymer material.

The invention is illustrated by the following Examples:

#### Example 1

(i) 2.68 gm of 2,6-dibromo-4-hydroxyphenol are added to a lye of 0.4 gm of sodium hydroxide in 40 ml of methanol. The methanol is removed and the solid is dried under vacuum. The dried solid is suspended in 50 ml of acetone and 1.21 gm (0.86 ml) of allyl bromide are added. The reaction mixture is heated to 40°C and held at that temperature for 1 hour. The

sodium bromide formed is filtered off and the acetone is removed under vacuum. The material formed is recrystallised from aqueous ethanol.

(ii) The above is repeated except that the dried solid is suspended in benzene and 0.9 gm of acryloyl chloride are added. The addition takes place at 5°C and the heating is started after the reaction has been left for 1 hour at room temperature.

(iii) 2.67 gm of 2,6-dibromo-4-aminophenol is dissolved in 50 ml of benzene. To this is added 0.9 gm of acryloyl chloride using the conditions above.

(iv) 21.4 gms of 2,4-dihydroxy-benzophenone are dissolved in a lye of 4.0 gms of sodium hydroxide in 60 mls. The solvent is removed and the monosodium compound is thoroughly dried, and suspended in 100 mls of benzene.

7.4 gms of acryloylchloride are added dropwise whilst the temperature is maintained at 5°C. The whole is then heated to 25°C and held for an hour, followed by 15 mins at reflux. The sodium chloride is filtered off and the solvent is removed by rotary evaporation. This leaves the acrylic ester as an oily residue which is recrystallised from aqueous ethanol to give yellow crystals.

The compounds prepared as described in procedures (i) to (iv) are incorporated into a hydrogel in the following manner:

The following purified and inhibitor free components are thoroughly mixed in the quantities indicated to ensure that no undissolved solids remain.

20	Acrylamide	3.6 g (25 pts)	20
	2-hydroxypropylacrylate	13.0 g (50 pts)	
	Ethylacrylate	5.0 g (25 pts)	
	Anti-bacterial monomer	0.42 g (2% by wt.)	
25	Azobisisobutyronitrile	0.042 g (0.2% by wt.)	25

The reactants are poured into lengths of polyethylene tubing sealed at one end. The system is then purged with nitrogen and sealed. The sealed tubes are placed in a water bath at 50°C for 72 hours and then postcured for 2 hours at 90°C in a vacuum oven. The polythene tubes are cut open to release the polymer rods. Optically clear lenses can be cut from the rods which on hydration remain clear. (The anti-bacterial monomer confers a faint yellow tinge visible in articles of thick cross-section.) The polymers have an equilibrium water content of 60% by weight and an oxygen permeability of  $155 \times 10^{-10}$  cc.mm.cm<sup>-2</sup>sec.<sup>-1</sup>cm.Hg<sup>-1</sup>.

Contact lenses cut from these materials and stored in aqueous solution partially open to the atmosphere show a markedly reduced tendency to sustain surface growth when compared to the unmodified polymer materials without the anti-bacterial substituent. After two months exposure, the unmodified polymer material has sustained a visible surface growth whereas the polymer materials with the antibacterial substituent are unaffected.

#### 40 Example 2 40

The following acid and inhibitor free monomers are charged into a 500 ml, three-necked flask containing 240 ml of dioxan:

45	2-hydroxy ethyl methacrylate	47.6 g (8 pts)	45
	ethyl hexylmethacrylate	7.92 g (1 pt)	
	styrene	4.16 g (1 pt)	
	anti-bacterial monomer prepared according to procedures (i) to (iv) of Example 1	0.54 g (1% by weight)	
50			50

The flask is equipped with a stirrer, thermometer, condenser, and a nitrogen bleed. The temperature of the reactants is raised to 40°C and 0.11 g (0.2% by weight) of azoisobutyronitrile in 10 ml of dioxan added.

The reactants are kept at 60°C for 8 hours. The contents of the flask are then cooled and added slowly to 2½ litres of diethyl ether to give a white precipitate which after filtering is washed with ether. The copolymer thus obtained is then dried under vacuum at 60°C. Finally, the copolymer is intimately mixed with a cross-linking agent and compression moulded at a temperature of 160°C to give an optically clear disc. A comparison of the discs so produced with an unmodified material shows again that polymer materials according to the present invention have a greatly reduced tendency to sustain surface growth of bacteria.

#### CLAIMS

1. A polymeric material suitable for use in biomedical applications, comprising a polymer having covalently bound to the polymer backbone substituents possessing anti-bacterial activity.
2. A polymeric material according to claim 1 wherein the polymer is derived from a non-

polar vinyl hydrocarbon monomer, a polar vinyl monomer and a monomer having a substituent possessing anti-bacterial activity.

3. A polymeric material according to claim 1 comprising units derived from:
  - 1) 20 to 40 mole % of a polymerisable amide which is an unsubstituted or substituted amide of a carboxylic acid containing olefinic unsaturation,
  - 2) 25 to 55 mole % of an N-vinyl lactam,
  - 3) 5 to 20 mole % of a polymerisable ester which is an ester of a carboxylic acid containing olefinic unsaturation,
  - 4) 1 to 10 mole % of a polymerisable carboxylic acid containing olefinic unsaturation,
  - 5) 3 to 10 mole % of a polymerisable hydrophobic vinyl monomer,
 and, either in addition to monomers (1) to (5) which total 100 mole % or in place of part of one or more of these, an ethylenically unsaturated monomer having a substituent possessing antibacterial activity or having a group onto which is subsequently grafted such a substituent, the copolymer being cross linked with a cross linking agent.
4. A polymeric material according to any one of the preceding claims derived from up to 15% by weight of an ethylenically unsaturated monomer having a substituent possessing anti-bacterial activity, based on the total weight of the other monomers.
5. A polymeric material according to any one of the preceding claims wherein the substituent possessing anti-bacterial activity is derived from a phenol substituted by alkyl, aralkyl, halogen, haloalkyl, haloaryl and/or amino, a polyhydric phenol unsubstituted or substituted by halogen, an acridine unsubstituted or substituted by amino, an aryl or aralkyl alcohol unsubstituted or substituted by halogen or an organic salt or other derivative of an organic or inorganic acid or amine.
6. A polymeric material according to claim 5 wherein the substituent possessing anti-bacterial activity is derived from 2, 6-dibromo-3 or 4-hydroxyphenol, 3-hydroxy-4-n-pentylphenol, 3-hydroxy-4-n-octylphenol, 4-chloro-2, 4-dihydroxy-diphenyl-methane, 2, 6-dibromo-4-aminophenol, 2, 4, 6-triaminophenol, 2, 6-diamino-4-n-pentyl-phenol, 2,6-dinitro-4-aminophenol, o-chloro-cresol, benzyl alcohol, phenyl ethyl alcohol, chlorbutanol, chlorhexidine diacetate, methyl, ethyl or propyl hydroxybenzoate, phenylmercuric acetate, benzalkonium chloride, ethylenediamino-tetraacetic acid, thiomersal or cetrimide.
7. A polymeric material according to any one of claims 3 to 6 wherein component (1) is acrylamide, methacrylamide or diacetone acrylamide or a mixture of two or all of these.
8. A polymeric material according to any one of claims 3 to 7 wherein component (2) is N-vinylpyrrolid-2-one.
9. A polymeric material according to any one of claims 3 to 8 wherein component (3) is a hydroxy substituted ester of acrylic or methacrylic acid.
10. A polymeric material according to any one of claims 3 to 9 wherein component (3) is hydroxy-propyl acrylate or hydroxy-ethyl methacrylate.
11. A polymeric material according to any one of claims 3 to 10 wherein component (4) is acrylic or methacrylic acid.
12. A polymeric material according to any one of claims 3 to 11 wherein component (5) is styrene or an ester of acrylic or methacrylic acid or a mixture thereof.
13. A polymeric material according to any one of the preceding claims cross linked with up to 5 weight % of a cross linking agent based on the total weight of the monomers.
14. A polymeric material according to any one of the preceding claims cross linked to the extent of one cross link to every 10 to 200 polymer units.
15. A polymeric material according to any one of the preceding claims wherein the cross linking agent is ethylene glycol dimethacrylate, a polyethylene oxide dimethacrylate, divinyl benzene, a diamide of an unsaturated aliphatic carboxylic acid, an anhydride of an aliphatic or aromatic carboxylic acid, a diepoxide or dicumyl peroxide.
16. A polymeric material according to claim 1 substantially as described in Example 1 or 2.
17. A polymeric material according to any one of the preceding claims in the form of a hydrogel containing 20% to 90% by weight of water.
18. A shaped article suitable for producing a contact lens, comprising a polymeric material as claimed in any one of the preceding claims.
19. A contact lens comprising a polymeric material as claimed in claim 17.
20. A process of preparing a polymeric material suitable for use in biomedical applications which comprises copolymerising at least two monomers one of which is an ethylenically unsaturated monomer having a substituent possessing anti-bacterial activity or having a group onto which is subsequently grafted such a substituent.
21. A process according to claim 20 wherein the polymeric material is as claimed in any one of claims 2 to 16.
22. A process according to claim 20 or 21 wherein the copolymerisation is performed in a mould to produce a shaped article.
23. A process according to claim 20 or 21 wherein a copolymer is produced in linear form



and is compression or injection moulded into a shaped article in the presence of a cross linking agent.

24. A process according to claim 22 or 23 wherein the shaped article is cut to form a contact lens.

5 25. A process according to claim 20 substantially as described in Example 1 or 2. 5

26. A process according to any one of claims 20 to 25 wherein the product is immersed in water or an aqueous medium until equilibrium is reached, to form a hydrogel.

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